

19. (PREVIOUSLY AMENDED) A method of inhibiting aggregation of a polypeptide comprising combining the polypeptide with a buffer comprising tris(hydroxymethyl)aminomethane (TRIS) mixed with a buffering molecule that does not contain a free amine group and which mitigates the change in pH that results from the formation of carbonic acid; zinc; and a phenolic preservative for a time and under conditions effective to inhibit aggregation.

20. (ORIGINAL) The method of claim 19, wherein the buffering molecule is selected from the group consisting of acetate, phosphate and citrate.

21. (PREVIOUSLY AMENDED) The method of claim 19, wherein the buffer further comprises an isotonicity agent.

22. (ORIGINAL) The method of claim 19, wherein the polypeptide is a monomeric insulin analog selected from the group consisting of LysB28ProB29-human insulin and AspB28 human insulin.

23. (ORIGINAL) The method of claim 22, wherein TRIS is present at a concentration of about 1.5 mg/ml to about 4.5 mg/ml; phosphate is present at a concentration of about 0.2 mg/ml to about 2.5 mg/ml, the monomeric insulin analog is present at a concentration of about 250 to about 1000 U/ml, zinc is present at a concentration of about .07  $\mu$ g/ml to about .09  $\mu$ g/ml, m-cresol is present at a concentration of about 2.2 mg/ml, phenol is present at a concentration of about 0.9 mg/ml and glycerol is the isotonicity agent and is present at a concentration of about 16 mg/ml.

24. (ORIGINAL) The method of claim 23, wherein TRIS is present at a concentration of about 2 mg/ml to about 3 mg/ml and phosphate is present at a concentration of about 0.5 mg/ml to about 1.5 mg/ml.

25. (NEW) A method of inhibiting aggregation of a polypeptide consisting essentially of combining the polypeptide with a buffer comprising tris(hydroxymethyl)aminomethane (TRIS)

08-13-2003 12:38PM FROM-Gates & Cooper LLP

+13106418798

T-060 P 006/013 F-082

mixed with a buffering molecule selected so that it does not contain a free amine group and which mitigates the change in pH that results from the formation of carbonic acid; zinc; and a phenolic preservative for a time and under conditions effective to inhibit aggregation.